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Hypercalcemic Nephropathy in the Dog

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INTRODUCTION

Calcium is a functionally important ion and coenzyme in most all of the body systems. Besides its structural role in bone, calcium is involved in muscle contraction, the blood coagulation system, enzyme activity, nerve impulse transmission, hormone release and membrane permeability.¹⁻³ Calcium metabolism is regulated primarily by parathyroid hormone (PTH), calcitonin (CT), and vitamin D (1,25-dihydroxycholecalciferol).^{1,2,4} The release of these hormones is controlled by the concentration of calcium in the plasma.⁵ Exact regulation of calcium in extracellular fluid is necessary to maintain normal body function.

The skeleton contains approximately 99 percent of the body's calcium stores. Only one percent of the total calcium is found outside the skeleton and one-tenth of one percent in the extracellular fluid.^{4,6} The extracellular pool of calcium is readily available for rapid exchange with intracellular stores.^{6,7} Total serum calcium (extra-cellular calcium) is present in three forms; protein-bound (50%), complexed (10%) and ionized calcium (40%).⁸ Ionized calcium is the biologically active fraction.^{6,9} In most cases, total serum calcium, not just ionized calcium, is measured due to the technical equipment required. Measurement of ionized calcium alone requires that blood be collected anaerobically and analyzed soon after collection.^{3,10} Ionized calcium values usually parallel changes in total calcium. It is necessary to interpret total serum calcium results in the context of the plasma albumin concentration and the acid-

base status of the animal.

The ratio of ionized calcium to protein-bound calcium is altered by fluctuations in acid-base balance. Alkalosis decreases the percentage of ionized calcium by increasing the protein-bound fraction. Acidosis increases the percentage of ionized calcium.^{3,6,11} Approximately one-half of the calcium bound is to protein, primarily albumin. Interpretation of total calcium depends on concurrent values for serum albumin and total protein.⁹ A positive linear relationship exists between total serum calcium and both serum total protein and albumin.^{3,12} In order to obtain more complete information about serum ionized calcium concentration, a correction formula for total serum calcium was derived on the basis of serum concentrations of albumin and total protein. The formula for calculating total serum calcium based on albumin concentrations is:

Adjusted calcium (mg/dl) =

Calcium (mg/dl) - Albumin (g/dl) + 3.5

The correction formula based on total serum protein concentration is:

Adjusted calcium (mg/dl) = Calcium (mg/dl) - 0.4 [Total Serum Protein (g/dl)] + 3.3

The correction formulas account for the effects of the quantity of protein,^{3,9} but not for the effects of acid-base fluctuations on protein-binding of calcium. Calcium-adjustment formulas can determine whether hypocalcemia or a hypercalcemia are masked by abnormal serum protein concentration.⁹ Hypoproteinemia can decrease the measured calcium, and hyperproteinemia will increase measured calcium.⁶ As serum protein concentrations decrease, more calcium is ionized and then removed from the serum by CT regulatory mechanisms. This results in an absolute decrease in serum calcium. Albumin is the most important calcium binder, binding approxi-

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mately 90 percent of the protein-bound calcium. Therefore, it is more advantageous to use the correcting formula based on albumin rather than total protein.^{3,6}

The normal total serum calcium value for the mature dog is approximately 10.0 mg/dl (9.4–12.2 mg/dl) with variations due to diet and analytical method.^{6,8,10} It is not unusual to see young, rapidly growing dogs with values approaching 12.0 mg/dl. General values for young dogs are approximately 11.1 ± 0.4 mg/dl (10.5 to 11.5 mg/dl).¹³ Older dogs (greater than eight years of age) may have normal serum calcium values of 9.0 mg/dl.⁸ There appears to be no breed- or sex-related differences in total serum calcium concentration. The total serum calcium concentration represents a balance between intestinal absorption, bone resorption and accretion, and renal excretion and reabsorption. Hypercalcemia exists when serum calcium levels rise above the normal value of 12 mg/dl.^{4,5,10,11} Persistent hypercalcemia is indicated by increased serum calcium concentration on two or more consecutive determinations and may indicate the presence of parathyroid, renal or neoplastic disease.^{2,13,14} Table 1 lists the differential diagnoses of symptomatic hypercalcemia in order of most likely occurrence.^{10,11,13}

TABLE 1.

Differential Diagnosis
1. Malignancy: Cancer-associated hypercalcemia
Lymphosarcoma
Adenocarcinoma (apocrine glands of the anal sac)
Other (Multiple myeloma, mammary tumors)
2. Hypoadrenocorticism
3. Renal failure
4. Bone lesion
Metastatic
Septic—bacterial or mycotic osteomyelitis
Disuse osteoporosis
5. Hypervitaminosis D
Iatrogenic—diet
Plants— <i>Cestrum diurnum</i>
<i>Solanum malacoxylon</i>
<i>Trisetum flavescens</i>
6. Primary hyperparathyroidism
Adenoma
Adenocarcinoma

PATHOGENESIS OF HYPERCALCEMIA

Neoplasia is the most common cause of hypercalcemia in the dog, with lymphosarcoma the most commonly involved tumor.^{5,10} Cancer-associated hypercalcemia, formerly referred to as pseudohyperparathyroidism, may be due to tumor metastases to the bone, concurrent parathyroid hyperplasia, or production of bone-resorbing factors by neoplastic cells.¹³ Hypercalcemia associated with tumors is usually caused by a malignant tumor of non-parathyroid origin secreting a factor or factors which mimic the action of PTH.^{5,6,12,15} There is no evidence radiographically or at necropsy of bone metastasis in this syndrome. Laboratory findings in cases of lymphosarcoma may show hypercalcemia, normo- or hypophosphatemia, azotemia, hypercalcinuria, hyperphosphaturia, and hyposthenuria.¹¹ The changes in calcium and phosphorus result from the action of PTH-like substances, but these substances are not inhibited by increases in serum calcium.^{10,15} It should be noted that it is important to measure and interpret serum calcium and phosphorus together, because their regulation and control are interrelated.⁶ Studies have identified several hypercalcemic factors produced by tumors: parathyroid hormone-like peptides,¹⁵ prostaglandin E₂,¹⁶ osteoclast-activating factor¹⁵ and non-vitamin D sterols.⁴ The chemical substances produced by tumors and the mechanisms by which hypercalcemia is induced are apparently different for different types of tumors.¹¹ Adenocarcinomas derived from apocrine glands of the anal sac are also an important cause of hypercalcemia in older female dogs.^{6,10,17} Other neoplasms which may be involved in this syndrome include testicular interstitial cell tumors and carcinoma of the mammary gland, stomach, thyroid and lung.^{5,10,12,15}

Hypoadrenocorticism (canine Addison's disease) results in hyperkalemia, hyponatremia and hypochloridemia due to decreased production of glucocorticoids and mineralocorticoids. In approximately 25 percent of the affected dogs, hypercalcemia will also be seen.¹³ The severity of hypercalcemia is correlated with the severity of hypoadrenocorticism. However, the hypercalcemia is usually mild, generally less than 13.5 mg/dl.^{13,18} The exact cause of the rise in calcium levels is unknown. Several mechanisms have been proposed, and the most likely explanation involves diminished renal excretion of calcium due to increased tubular

reabsorption of calcium.¹⁸ Hypercalcemia associated with hypoadrenocorticism usually offers a good prognosis because it is corrected following adequate corticosteroid therapy for the hypoadrenocorticism.

Primary and secondary bone tumors and septic osteomyelitis are uncommon causes of hypercalcemia in the dog, but are seen more often in man as a mechanism of hypercalcemia.¹⁹ Primary or secondary bone tumors may cause hypercalcemia via osteolysis of the bone. It has been hypothesized that there is increased resorption of bone without adequate compensatory urinary excretion of calcium.¹³ Associated with changes in calcium are normal or moderately elevated serum phosphorus and alkaline phosphatase.^{4,10} These changes are the result of either mechanical destruction by the infiltrating tumor or by bone-resorbing factors such as prostaglandins or osteoclast-activating factor.⁴ Primary tumors which may produce hypercalcemia include osteosarcoma and multiple myeloma.⁴ Mammary gland, liver, lung and prostate carcinomas have the highest incidence of secondary bone tumors in the dog.¹³ Bacterial and mycotic osteomyelitis (histoplasmosis, coccidioidomycosis and blastomycosis) may also produce a hypercalcemic state.¹³ Bone changes are due to either sepsis and inflammation resulting in bone destruction; or production of bone-resorbing factors.¹⁰

Primary hyperparathyroidism is uncommon in animals. Most likely findings include a single functional adenoma of the parathyroid gland, which results in production of an excess amount of PTH. Blood chemistry findings include marked elevation of serum calcium, a decrease in phosphorus and an increase in serum alkaline phosphatase activity.⁶ There are usually radiographic changes indicating demineralization, subperiosteal areas of cortical bone resorption, loss of lamina dura dentes, soft tissue mineralization and bone cysts.^{4,6,10}

Primary Renal Disease

Primary renal disease, chronic or acute, can cause a hypercalcemic condition. However, it is often difficult to establish if the hypercalcemia is the cause of renal disease or the result of renal dysfunction.⁶ Hypercalcemia is not a classic finding in chronic renal failure. Serum biochemistries show a normal to low calcium, increased phosphorus and increased serum concentrations of PTH.²⁰ These dogs are usually azotemic.¹³ In five to ten percent of the

dogs with chronic renal failure, calcium levels are 12.0 mg/dl or greater.¹⁰ The pathogenesis of hypercalcemia induced by primary renal disease is not fully understood, and several mechanisms have been proposed: a) decreased excretion of calcium by the diseased kidney; b) decreased renal tubular degradation of PTH; c) PTH-induced hypercalcemia which increases complexed calcium; d) overcompensation by the parathyroid gland; and e) exaggerated response to vitamin D with resultant increase in intestinal absorption of calcium.¹⁰ It now appears that the parathyroid glands and increased concentration of PTH are important in pathogenesis of hypercalcemia associated with chronic renal failure.¹³

Acute renal failure and hypercalcemia in man may often be preceded by rhabdomyolysis.^{4,20} Rhabdomyolysis and associated hypercalcemia is rarely observed in dogs. In man, rhabdomyolysis will cause an acute tubular necrosis.²⁰ The causes of rhabdomyolysis in man include traumatic, drug-induced, association with malignant hyperthermia or idiopathic.²¹ In a case reported in a dog, traumatic damage to muscle resulted in dystrophic calcification of the muscle.⁴ Damaged muscle is the site for calcium deposition during the oliguric phase of acute renal failure.²⁰ During the diuretic phase, the sequestered calcium is released from the tissues leading to hypercalcemia and hyperphosphatemia.^{10,20} The release of a large amount of calcium may overwhelm the capacity of the kidneys to excrete calcium.

Clinical Signs

Hypercalcemia causes a variety of clinical signs because it affects four major body systems: renal, gastrointestinal, nervous and muscular. The structural and functional effects of hypercalcemia depend upon the underlying cause and the duration and severity of the hypercalcemia.

Gastrointestinal dysfunction is the result of decreased contractility of the smooth muscle. This may cause anorexia, vomiting and constipation.^{4,6,15} Constipation may also result from reduced food and water intake and dehydration. Polydipsia and polyuria are also potential signs of hypercalcemia due to ADH inhibition at the collecting tubules of the renal medulla.

The nervous system is affected because hypercalcemia depresses the excitability of nervous tissue and suppresses lower motor neuron activity.^{10,15} Behavioral changes, depression,

muscle twitching, or seizures may be seen.^{10,16} Depression is the most common neurologic change seen in dogs. In severe cases, a dog may be in a stupor or coma. Mild or chronic hypercalcemia may produce no neurologic abnormalities.⁶

Both skeletal and cardiac muscles can be affected. There is a general muscular weakness due to a decrease in muscle tone and there may be specific cardiac changes due to the hypercalcemia. Mild hypercalcemia may cause only hypertension.^{20,21} With moderate to severe hypercalcemia, there may be arrhythmias, shortening of the Q-T interval, and prolongation of the P-R interval seen on electrocardiograms.^{19,21} In severe cases, premature ventricular contractions or ventricular tachycardia may be seen.⁴ Cardiac and renal tissues may also undergo mineralization. Hypertension, documented in man but not yet in dogs, may be the result of hypercalcemic nephropathy, but is also seen when renal function is normal. Proposed mechanisms for hypertension include: a) direct or indirect effect of calcium on peripheral resistance; b) increased cardiac output due to the positive inotropic effect of calcium; or c) changes in the renin-angiotensin system.²¹

NORMAL KIDNEY FUNCTION AND CALCIUM

The kidney is intimately involved in the regulation of serum calcium. Calcium absorption and excretion are under the influence of hormonal regulation. The amount of calcium in extracellular fluid, cells, and bone is primarily dependent on the amounts absorbed in the intestine and excreted by the kidney.¹⁹ Maintenance of serum calcium levels is controlled by PTH, vitamin D, and target organ activity. Parathyroid hormone is secreted in response to fluctuations in ionized calcium and acts on bone and the kidney. Parathyroid hormone is also important in the formation of 1,25-dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$) from 25-hydroxycholecalciferol ($25(\text{OH})\text{D}_3$) by the renal cortex.¹⁹ 1,25-dihydroxycholecalciferol is the active form of vitamin D at the intestine where it promotes absorption of calcium and phosphate. This compound also has a role in both bone resorption and bone deposition. Without vitamin D, there is a decrease in the effect of PTH on bone resorption. Renal activation of vitamin D is increased by PTH or a decrease in plasma phosphate. It is suppressed

by hypercalcemia. Since a fall in plasma calcium will cause an increase in PTH secretion and concomitant increase in active vitamin D, the kidney has an important role in the regulation of serum calcium concentration.^{19,22}

Short-term calcium concentration is controlled primarily by the effect of PTH on bone resorption. Long-term control results from the effect of PTH on reabsorption of calcium from kidney tubules and absorption of calcium via the gastrointestinal mucosa.²³ In the kidney, most of the serum calcium in the glomerular filtrate is reabsorbed in the proximal tubules and ascending limb of the loop of Henle.^{19,23,24} In the distal tubules and collecting tubules the reabsorption of calcium becomes selective. This is most likely the site for independent regulation of calcium.²³ Parathyroid hormones will stimulate tubular calcium reabsorption and decrease phosphate reabsorption by activation of adenyl cyclase, to increase production of cyclic AMP. Parathyroid hormone has also been shown to alter renal blood flow and glomerular filtration rate.⁷

HYPERCALCEMIC NEPHROPATHY

Increases in calcium can cause both structural and functional changes in the kidney. One of the earliest clinical manifestations of hypercalcemia is hyposthenuric polyuria with a compensatory polydipsia. The urine is hyposthenuric because calcium interferes with the normal response of the collecting tubules to antidiuretic hormone (ADH), thereby causing impairment of renal concentrating ability. One mechanism of calcium interference with ADH shows calcium damaging ADH receptors in the collecting tubules. This results in a decrease of ADH-binding.¹⁰ Calcium also disrupts assembly of cytoplasmic microtubules. It is postulated that these tubules are necessary to bring forth the hydrosmotic effects of ADH. With a decrease in these microtubules, water movement from the collecting duct lumen to the interstitium is impeded.²⁵ The result is a hyposthenuric polyuria that is resistant to the effects of exogenous ADH^{15,9} indicating that the hyposthenuria is renal in origin.¹⁵

Calcium is antagonistic to the adenyl cyclase-cyclic AMP system. Hypercalcemia decreases cyclic AMP formation (via adenyl cyclase) in the distal convoluted tubules and collecting ducts.^{4,26} A decrease in cyclic AMP decreases the response to ADH. Calcium also inhibits the Na-K ATPase required for active

transport of sodium or chloride into the renal medullary interstitium.¹⁰ This can result in inhibition of active transport of sodium chloride into the interstitium from the thick ascending limb of the loop of Henle and the distal tubules and collecting ducts.²⁵ With diminished sodium chloride reabsorption, there is a decrease in water reabsorption. Increased urine flow and sodium chloride loss, lead to hypovolemia.²⁵ The decreased response to ADH prevents urea accumulation in the inner medulla, which contributes to the concentrating defect.¹⁹ During this phase of polyuria and polydipsia, there is no elevation of blood urea nitrogen (BUN) or creatinine. If azotemia is present it may be due to; prerenal factors such as dehydration from anorexia, vomiting, or water diuresis; or, renal factors such as a decrease in renal perfusion or intrarenal hydronephrosis.¹⁰

Renal failure initially can result from predominantly prerenal factors, but if hypercalcemia persists, the renal failure may be due primarily to acquired intrinsic renal tubular lesions.⁵ Effects of hypercalcemia on the kidney may range from mild and reversible damage to severe and progressive damage. Injury to renal tubular epithelium may be due to the direct toxic effect of increased calcium in serum and filtered tubular fluid. Calcium may also cause vasoconstriction of renal vessels (afferent arterioles) resulting in ischemia and decreased renal blood flow.^{10,25}

Initial injury results in focal degeneration in the ascending loop of Henle, distal convoluted tubule and collecting duct. Medullary structures (loops of Henle and collecting ducts) are involved first; probably because of higher medullary calcium concentrations.¹⁹ Earliest changes are at the intracellular level: mitochondrial distortion and injury in tubular epithelial cells. Calcification begins with deposition of calcium-phosphorus complexes in the mitochondria. These complexes disrupt cell function and can lead to cell necrosis.¹⁰ Basement membranes also become thickened and mineralized. A significant amount of tubular damage may occur without histologically demonstrable precipitates of calcium.¹² In the early stages of hypercalcemia, glomeruli are not involved. If tubular basement membranes have not been damaged, the chances for reversal of renal damage are good, assuming the cause of the hypercalcemia can be identified and eliminated.⁴

Cast formation results from desquamated,

necrotic epithelial cells. These cells form casts which may become mineralized and obstruct the tubular lumen. Obstruction by calcium concretions predisposes to infection and focal pyelonephritis.^{10,12} Calcified cellular debris may cause obstructive atrophy of nephrons.²⁷ Damage to tubular basement membranes and cast formation markedly diminishes the ability of the kidney to regenerate.⁴

As hypercalcemic damage progresses, there is increased mineralization of tubular epithelium and basement membranes. Pathologic changes can be seen interstitially and within the tubules. These changes affect the distal tubules and collecting ducts.²¹ The reversibility of renal damage depends on the extent of renal mineralization, the presence of intact tubular basement membranes and adequate numbers of remaining viable nephrons.⁶ Advanced stages of severe or prolonged hypercalcemia are characterized by mineralization throughout the renal parenchyma, glomerular capillaries, Bowman's capsules and walls of vessels.^{12,15} Eventually, there is fibroblastic proliferation and infiltration with chronic inflammatory cells.²¹ This leads to interstitial scarring and calcification, the hallmark of irreversible damage.¹⁹

As mentioned previously, polyuria and polydipsia are often the earliest recognized clinical signs. Hypercalcemia affects the glomerulus by causing a decrease in glomerular filtration rate. The decrease in GFR may be the result of calcium-associated changes in glomerular capillary permeability or volume contraction secondary to fluid losses.⁶ A decrease in GFR may also be due to an increase in PTH.²⁴ Hypercalcemia affects the loop of Henle by inhibiting calcium and magnesium reabsorption. In the distal tubules and collecting ducts there is selective impairment of calcium reabsorption²⁴ in addition to the effects of calcium on ADH. As damage progresses, renal insufficiency becomes apparent. There is a continued decrease in GFR with a subsequent increase in BUN and creatinine levels. With progressive reduction in GFR, there is an increase in serum phosphorus and a decrease in urine calcium concentration.

In determining renal involvement and establishing a diagnosis and a plan for treatment, it is necessary to evaluate several biochemical tests. Serum calcium should be repeated to rule out sample errors or changes due to the age of the dog and concentrations of albumin and

protein.¹³ A complete blood count, complete serum chemistries, and electrolytes are helpful in ruling on several of the differential diagnoses. Chemistries should include serum phosphorus, BUN, creatinine and serum alkaline phosphatase. A urinalysis can reveal glucosuria and proteinuria due to decreased tubular function, besides measuring specific gravity.⁶ Other tests which are helpful in establishing a diagnosis include radiographic exam, electrocardiographic exam and possible biopsy. Table 2 lists laboratory results and gross findings for the differential diagnosis of hypercalcemia.

Once the serum calcium is restored to normal, treatment of the primary problem is indicated.

Management of concomitant renal failure includes maintenance of adequate fluid and electrolyte balance, prevention of dehydration due to diuretic use, and correction of acid-base imbalances.^{4,10} By maintaining adequate renal perfusion, the chances of ischemic damage to nephrons is decreased. No therapy will eliminate renal lesions already present. If the hypercalcemia can be controlled and the dog kept alive long enough, tubular damage may be repaired by regeneration and functional adaptation.¹⁰

TABLE 2. Differential Diagnosis of Hypercalcemia by Laboratory Tests and Gross Findings.¹⁰

Disease	Serum Calcium	Serum Phosphorus	SAP	Bone Lesion	Soft Tissue Mineralization	Parathyroid Lesion
Primary hyperthyroidism	High	Low	Elevated	Severe, generalized	Moderate	Adenoma
Malignancy	High	Low	Normal or slightly elevated	Mild, generalized	Moderate	Carcinoma
Osteolytic bone tumor	High	Normal or high	Moderately elevated	Focal, multifocal	Moderate	Inactivity or atrophy
Vitamin D intoxication	High	High	Normal	Mild or absent	Moderate	Inactivity or atrophy

TREATMENT

Fluid volume expansion is the best symptomatic treatment for hypercalcemia.¹³ Since many of the effects of hypercalcemia are accentuated by dehydration, disturbances in fluid balance should be corrected in all cases.^{4,10} Fluid therapy with 0.9 percent sodium chloride intravenously will promote urinary excretion of calcium.²¹ In cases of mild hypercalcemia (less than 14 mg/dl), fluid replacement may be all that is necessary to decrease serum calcium. When calcium levels are greater than 14 mg/dl, diuretics such as furosemide or ethacrynic acid are effective as calciuretic agents. It is important to maintain adequate extracellular fluid volume while using these diuretics. Thiazide diuretics should not be used because they reduce urinary excretion of calcium.²¹ Glucocorticoids may be effective in lowering serum calcium concentration by blocking calcium absorption from the small intestine and increasing the renal excretion of calcium.⁴ In cases where the calcium levels exceed 16 mg/dl, sodium bicarbonate given intravenously may reduce the toxic effects of the calcium.

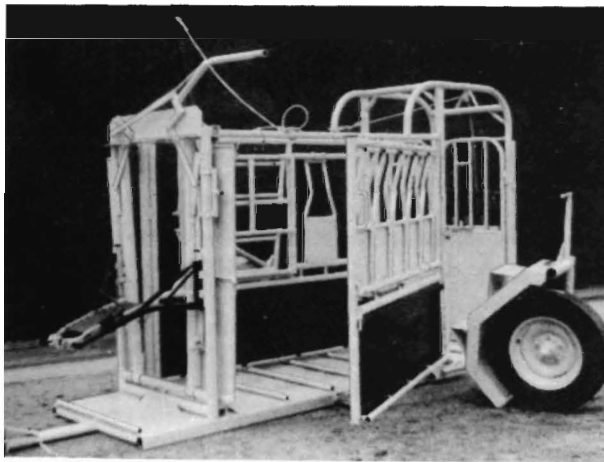
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